HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ONGLYZA safely and effectively. See full prescribing information for ONGLYZA.

ONGLYZA® (saxagliptin) tablets, for oral use
Initial U.S. Approval: 2009

---------- **RECENT MAJOR CHANGES** ----------

Warnings and Precautions	
Pancreatitis (5.1)	4/2016
Heart Failure (5.2)	4/2016
Bullous Pemphigoid (5.6)	1/2017

---------- **INDICATIONS AND USAGE** ----------

ONGLYZA is a dipeptidyl peptidase-4 (DPP4) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1.1, 14)
Limitation of use:

- Not used for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis. (1.2)

---------- **DOSAGE AND ADMINISTRATION** ----------

- Recommended dosage is 2.5 mg or 5 mg once daily taken regardless of meals. (2.1)
- Patients with moderate or severe renal impairment, or end-stage renal disease (CrCl ≤50 mL/min): Recommended dosage is 2.5 mg once daily regardless of meals. (2.2)
- Assess renal function before starting ONGLYZA and periodically thereafter. (2.2)
- 2.5 mg daily is recommended for patients also taking strong cytochrome P450 3A4/5 (CYP3A4/5) inhibitors (e.g., ketoconazole). (2.3, 7.1)

---------- **DOSAGE FORMS AND STRENGTHS** ----------

- Tablets: 5 mg and 2.5 mg. (3)

---------- **CONTRAINDICATIONS** ----------

- History of a serious hypersensitivity reaction (e.g., anaphylaxis, angioedema, exfoliative skin conditions) to ONGLYZA. (4)

---------- **WARNINGS AND PRECAUTIONS** ----------

- *Pancreatitis:* If pancreatitis is suspected, promptly discontinue ONGLYZA. (5.1)
- *Heart Failure:* Consider the risks and benefits of ONGLYZA in patients who have known risk factors for heart failure. Monitor patients for signs and symptoms. (5.2)
- *Hypoglycemia:* In add-on to sulfonylurea, add-on to insulin, and add-on to metformin plus sulfonylurea trials, confirmed hypoglycemia was more common in patients treated with ONGLYZA compared to placebo. When used with an insulin secretagogue (e.g., sulfonylurea) or insulin, a lower dose of insulin secretagogue or insulin may be required to minimize the risk of hypoglycemia. (5.3, 6.1)
- *Hypersensitivity-Related Events (e.g., urticaria, facial edema):* More common in patients treated with ONGLYZA than in patients treated with placebo; and postmarketing reports of serious hypersensitivity reactions such as anaphylaxis, angioedema, and exfoliative skin conditions. Promptly discontinue ONGLYZA, assess for other potential causes, institute appropriate monitoring and treatment, and initiate alternative treatment for diabetes. (5.4, 6.1, 6.2)
- *Arthralgia*: Severe and disabling arthralgia has been reported in patients taking DPP4 inhibitors. Consider as a possible cause for severe joint pain and discontinue drug if appropriate. (5.5)
- *Bullous Pemphigoid*: There have been postmarketing reports of bullous pemphigoid requiring hospitalization in patients taking DPP-4 inhibitors. Tell patients to report development of blisters or erosions. If bullous pemphigoid is suspected, discontinue ONGLYZA. (5.6)
- *Macrovascular Outcomes:* There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with ONGLYZA or any other antidiabetic drug. (5.7)

---------- **ADVERSE REACTIONS** ----------

- Adverse reactions reported in ≥5% of patients treated with ONGLYZA and more commonly than in patients treated with placebo are upper respiratory tract infection, urinary tract infection, and headache. (6.1)
- Peripheral edema was reported more commonly in patients treated with the combination of ONGLYZA and a thiazolidinedione (TZD) than in patients treated with the combination of placebo and TZD. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact AstraZeneca at 1-800-236-9933 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

---------- **DRUG INTERACTIONS** ----------

- *Strong CYP3A4/5 inhibitors (e.g., ketoconazole)*: Coadministration with ONGLYZA significantly increases saxagliptin concentrations. Recommend limiting ONGLYZA dosage to 2.5 mg once daily. (2.3, 7.1)

---------- **USE IN SPECIFIC POPULATIONS** ----------

- No adequate and well-controlled studies in pregnant women. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 1/2017

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Monotherapy and Combination Therapy

ONGLYZA is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus [*see Clinical Studies (14)*].

1.2 Limitation of Use

ONGLYZA is not indicated for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis, as it would not be effective in these settings.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of ONGLYZA is 2.5 mg or 5 mg once daily taken regardless of meals. ONGLYZA tablets must not be split or cut.

2.2 Dosage in Patients with Renal Impairment

No dosage adjustment for ONGLYZA is recommended for patients with mild renal impairment (creatinine clearance [CrCl] >50 mL/min).

The dosage of ONGLYZA is 2.5 mg once daily (regardless of meals) for patients with moderate or severe renal impairment, or with end-stage renal disease (ESRD) requiring hemodialysis (creatinine clearance [CrCl] ≤50 mL/min) [*see Clinical Pharmacology (12.3) and Clinical Studies (14.2)*]. ONGLYZA should be administered following hemodialysis. ONGLYZA has not been studied in patients undergoing peritoneal dialysis.

Because the dosage of ONGLYZA should be limited to 2.5 mg based upon renal function, assessment of renal function is recommended prior to initiation of ONGLYZA and periodically thereafter. Renal function can be estimated from serum creatinine using the Cockcroft-Gault formula or Modification of Diet in Renal Disease formula [*see Clinical Pharmacology (12.3)*].

2.3 Dosage Adjustment with Concomitant Use of Strong CYP3A4/5 Inhibitors

The dosage of ONGLYZA is 2.5 mg once daily when coadministered with strong cytochrome P450 3A4/5 (CYP3A4/5) inhibitors (e.g., ketoconazole, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin) [*see Drug Interactions (7.1) and Clinical Pharmacology (12.3)*].

2.4 Concomitant Use with an Insulin Secretagogue (e.g., Sulfonylurea) or with Insulin

When ONGLYZA is used in combination with an insulin secretagogue (e.g., sulfonylurea) or with insulin, a lower dose of the insulin secretagogue or insulin may be required to minimize the risk of hypoglycemia [*see Warnings and Precautions (5.3)*].

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3 DOSAGE FORMS AND STRENGTHS

- ONGLYZA (saxagliptin) 5 mg tablets are pink, biconvex, round, film-coated tablets with “5” printed on one side and “4215” printed on the reverse side, in blue ink.
- ONGLYZA (saxagliptin) 2.5 mg tablets are pale yellow to light yellow, biconvex, round, film-coated tablets with “2.5” printed on one side and “4214” printed on the reverse side, in blue ink.

4 CONTRAINDICATIONS

ONGLYZA is contraindicated in patients with a history of a serious hypersensitivity reaction to ONGLYZA, such as anaphylaxis, angioedema, or exfoliative skin conditions [*see Warnings and Precautions (5.4) and Adverse Reactions (6.2)*].

5 WARNINGS AND PRECAUTIONS

5.1 Pancreatitis

There have been postmarketing reports of acute pancreatitis in patients taking ONGLYZA. In a cardiovascular outcomes trial enrolling participants with established atherosclerotic cardiovascular disease (ASCVD) or multiple risk factors for ASCVD (SAVOR trial), cases of definite acute pancreatitis were confirmed in 17 of 8240 (0.2%) patients receiving ONGLYZA compared to 9 of 8173 (0.1%) receiving placebo. Preexisting risk factors for pancreatitis were identified in 88% (15/17) of those patients receiving ONGLYZA and in 100% (9/9) of those patients receiving placebo.

After initiation of ONGLYZA, observe patients for signs and symptoms of pancreatitis. If pancreatitis is suspected, promptly discontinue ONGLYZA and initiate appropriate management. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using ONGLYZA.

5.2 Heart Failure

In a cardiovascular outcomes trial enrolling participants with established ASCVD or multiple risk factors for ASCVD (SAVOR trial), more patients randomized to ONGLYZA (289/8280, 3.5%) were hospitalized for heart failure compared to patients randomized to placebo (228/8212, 2.8%). In a time-to-first-event analysis the risk of hospitalization for heart failure was higher in the ONGLYZA group (estimated Hazard Ratio: 1.27; 95% CI: 1.07, 1.51). Subjects with a prior history of heart failure and subjects with renal impairment had a higher risk for hospitalization for heart failure, irrespective of treatment assignment.

Consider the risks and benefits of ONGLYZA prior to initiating treatment in patients at a higher risk for heart failure. Observe patients for signs and symptoms of heart failure during therapy. Advise patients of the characteristic symptoms of heart failure and to immediately report such symptoms. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation of ONGLYZA.

5.3 Hypoglycemia with Concomitant Use of Sulfonylurea or Insulin

When ONGLYZA was used in combination with a sulfonylurea or with insulin, medications known to cause hypoglycemia, the incidence of confirmed hypoglycemia was increased over that of placebo used in combination with a sulfonylurea or with insulin [*see Adverse Reactions (6.1)*]. Therefore, a lower dose of the insulin secretagogue or insulin may be required to minimize the risk of hypoglycemia when used in combination with ONGLYZA [*see Dosage and Administration (2.4)*].

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5.4 Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with ONGLYZA. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions. Onset of these reactions occurred within the first 3 months after initiation of treatment with ONGLYZA, with some reports occurring after the first dose.

If a serious hypersensitivity reaction is suspected, discontinue ONGLYZA, assess for other potential causes for the event, and institute alternative treatment for diabetes [*see Adverse Reactions (6.2)*].

Use caution in a patient with a history of angioedema to another dipeptidyl peptidase-4 (DPP4) inhibitor because it is unknown whether such patients will be predisposed to angioedema with ONGLYZA.

5.5 Severe and Disabling Arthralgia

There have been postmarketing reports of severe and disabling arthralgia in patients taking DPP4 inhibitors. The time to onset of symptoms following initiation of drug therapy varied from one day to years. Patients experienced relief of symptoms upon discontinuation of the medication. A subset of patients experienced a recurrence of symptoms when restarting the same drug or a different DPP4 inhibitor. Consider DPP4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate.

5.6 Bullous Pemphigoid

Postmarketing cases of bullous pemphigoid requiring hospitalization have been reported with DPP-4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor. Tell patients to report development of blisters or erosions while receiving ONGLYZA. If bullous pemphigoid is suspected, ONGLYZA should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

5.7 Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with ONGLYZA or any other antidiabetic drug.

6 ADVERSE REACTIONS

The following serious adverse reactions are described below or elsewhere in the prescribing information:

- Pancreatitis [*see Warnings and Precautions (5.1)*]
- Heart Failure [*see Warnings and Precautions (5.2)*]
- Hypoglycemia with Concomitant Use of Sulfonylurea or Insulin [*see Warnings and Precautions (5.3)*]
- Hypersensitivity Reactions [*see Warnings and Precautions (5.4)*]
- Severe and disabling arthralgia [*see Warnings and Precautions (5.5)*]
- Bullous pemphigoid [*see Warnings and Precautions (5.6)*]

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6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse Reactions in Efficacy Trials

The data in Table 1 are derived from a pool of 5 placebo-controlled clinical trials [*see Clinical Studies (14)*]. These data shown in the table reflect exposure of 882 patients to ONGLYZA and a mean duration of exposure to ONGLYZA of 21 weeks. The mean age of these patients was 55 years, 1.4 % were 75 years or older and 48.4% were male. The population was 67.5% White, 4.6% Black or African American, 17.4% Asian, Other 10.5% and 9.8% were of Hispanic or Latino ethnicity. At baseline the population had diabetes for an average of 5.2 years and a mean HbA1c of 8.2%. Baseline estimated renal function was normal or mildly impaired (eGFR≥60mL/min/1.73m^2) in 91% of these patients.

Table 1 shows common adverse reactions, excluding hypoglycemia, associated with the use of ONGLYZA. These adverse reactions occurred more commonly on ONGLYZA than on placebo and occurred in at least 5% of patients treated with ONGLYZA.

Table 1: Adverse Reactions in Placebo-Controlled Trials* Reported in ≥5% of Patients Treated with ONGLYZA 5 mg and More Commonly than in Patients Treated with Placebo

	% of Patients	
	ONGLYZA 5 mg N=882	**Placebo N=799**
Upper respiratory tract infection	7.7	7.6
Urinary tract infection	6.8	6.1
Headache	6.5	5.9

* The 5 placebo-controlled trials include two monotherapy trials and one add-on combination therapy trial with each of the following: metformin, thiazolidinedione, or glyburide. Table shows 24-week data regardless of glycemic rescue.

In patients treated with ONGLYZA 2.5 mg, headache (6.5%) was the only adverse reaction reported at a rate ≥5% and more commonly than in patients treated with placebo.

In the add-on to TZD trial, the incidence of peripheral edema was higher for ONGLYZA 5 mg versus placebo (8.1% and 4.3%, respectively). The incidence of peripheral edema for ONGLYZA 2.5 mg was 3.1%. None of the reported adverse reactions of peripheral edema resulted in study drug discontinuation. Rates of peripheral edema for ONGLYZA 2.5 mg and ONGLYZA 5 mg versus placebo were 3.6% and 2% versus 3% given as monotherapy, 2.1% and 2.1% versus 2.2% given as add-on therapy to metformin, and 2.4% and 1.2% versus 2.2% given as add-on therapy to glyburide.

The incidence rate of fractures was 1.0 and 0.6 per 100 patient-years, respectively, for ONGLYZA (pooled analysis of 2.5 mg, 5 mg, and 10 mg) and placebo. The 10 mg dosage is not an approved dosage. The incidence rate of fracture events in patients who received ONGLYZA did not increase over time. Causality has not been established and nonclinical studies have not demonstrated adverse effects of ONGLYZA on bone.

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An event of thrombocytopenia, consistent with a diagnosis of idiopathic thrombocytopenic purpura, was observed in the clinical program. The relationship of this event to ONGLYZA is not known.

Discontinuation of therapy due to adverse reactions occurred in 2.2%, 3.3%, and 1.8% of subjects receiving ONGLYZA 2.5 mg, ONGLYZA 5 mg, and placebo, respectively. The most common adverse reactions (reported in at least 2 subjects treated with ONGLYZA 2.5 mg or at least 2 subjects treated with ONGLYZA 5 mg) associated with premature discontinuation of therapy included lymphopenia (0.1% and 0.5% versus 0%, respectively), rash (0.2% and 0.3% versus 0.3%), blood creatinine increased (0.3% and 0% versus 0%), and blood creatine phosphokinase increased (0.1% and 0.2% versus 0%).

Adverse Reactions with Concomitant Use with Insulin

In the add-on to insulin trial [*see Clinical Studies (14.1)*], the incidence of adverse events, including serious adverse events and discontinuations due to adverse events, was similar between ONGLYZA and placebo, except for confirmed hypoglycemia [*see Adverse Reactions (6.1)*].

Hypoglycemia

Adverse reactions of hypoglycemia were based on all reports of hypoglycemia. A concurrent glucose measurement was not required or was normal in some patients. Therefore, it is not possible to conclusively determine that all these reports reflect true hypoglycemia.

In the add-on to glyburide study, the overall incidence of reported hypoglycemia was higher for ONGLYZA 2.5 mg and ONGLYZA 5 mg (13.3% and 14.6%) versus placebo (10.1%). The incidence of confirmed hypoglycemia in this study, defined as symptoms of hypoglycemia accompanied by a fingerstick glucose value of ≤50 mg/dL, was 2.4% and 0.8% for ONGLYZA 2.5 mg and ONGLYZA 5 mg and 0.7% for placebo [*see Warnings and Precautions (5.3)*]. The incidence of reported hypoglycemia for ONGLYZA 2.5 mg and ONGLYZA 5 mg versus placebo given as monotherapy was 4% and 5.6% versus 4.1%, respectively, 7.8% and 5.8% versus 5% given as add-on therapy to metformin, and 4.1% and 2.7% versus 3.8% given as add-on therapy to TZD. The incidence of reported hypoglycemia was 3.4% in treatment-naive patients given ONGLYZA 5 mg plus metformin and 4% in patients given metformin alone.

In the active-controlled trial comparing add-on therapy with ONGLYZA 5 mg to glipizide in patients inadequately controlled on metformin alone, the incidence of reported hypoglycemia was 3% (19 events in 13 patients) with ONGLYZA 5 mg versus 36.3% (750 events in 156 patients) with glipizide. Confirmed symptomatic hypoglycemia (accompanying fingerstick blood glucose ≤50 mg/dL) was reported in none of the ONGLYZA-treated patients and in 35 glipizide-treated patients (8.1%) ($p<0.0001$).

In the add-on to insulin trial, the overall incidence of reported hypoglycemia was 18.4% for ONGLYZA 5 mg and 19.9% for placebo. However, the incidence of confirmed symptomatic hypoglycemia (accompanying fingerstick blood glucose ≤50 mg/dL) was higher with ONGLYZA 5 mg (5.3%) versus placebo (3.3%).

In the add-on to metformin plus sulfonylurea trial, the overall incidence of reported hypoglycemia was 10.1% for ONGLYZA 5 mg and 6.3% for placebo. Confirmed hypoglycemia was reported in 1.6% of the ONGLYZA-treated patients and in none of the placebo-treated patients [*see Warnings and Precautions (5.3)*].

Hypersensitivity Reactions

Hypersensitivity-related events, such as urticaria and facial edema in the 5-study pooled analysis up to Week 24 were reported in 1.5%, 1.5%, and 0.4% of patients who received ONGLYZA 2.5 mg, ONGLYZA 5 mg, and placebo, respectively. None of these events in patients who received ONGLYZA required hospitalization or were reported as life-threatening by the investigators. One ONGLYZA-treated patient in this pooled analysis discontinued due to generalized urticaria and facial edema.

Renal Impairment

In the SAVOR trial, adverse reactions related to renal impairment, including laboratory changes (i.e., doubling of serum creatinine compared with baseline and serum creatinine >6 mg/dL), were reported in 5.8% (483/8280) of ONGLYZA-treated subjects and 5.1% (422/8212) of placebo-treated subjects. The most frequently reported adverse reactions included renal impairment (2.1% vs. 1.9%), acute renal failure (1.4% vs. 1.2%), and renal failure (0.8% vs. 0.9%), in the ONGLYZA versus placebo groups, respectively. From baseline to the end of treatment, there was a mean decrease in eGFR of 2.5 mL/min/1.73m^2 for ONGLYZA-treated patients and a mean decrease of 2.4 mL/min/1.73m^2 for placebo-treated patients. More subjects randomized to ONGLYZA (421/5227, 8.1%) compared to subjects randomized to placebo (344/5073, 6.8%) had downward shifts in eGFR from >50 mL/min (i.e., normal or mild renal impairment) to ≤50 mL/min (i.e., moderate or severe renal impairment). The proportions of subjects with renal adverse reactions increased with worsening baseline renal function and increased age, regardless of treatment assignment.

Infections

In the unblinded, controlled, clinical trial database for ONGLYZA to date, there have been 6 (0.12%) reports of tuberculosis among the 4959 ONGLYZA-treated patients (1.1 per 1000 patient-years) compared to no reports of tuberculosis among the 2868 comparator-treated patients. Two of these six cases were confirmed with laboratory testing. The remaining cases had limited information or had presumptive diagnoses of tuberculosis. None of the six cases occurred in the United States or in Western Europe. One case occurred in Canada in a patient originally from Indonesia who had recently visited Indonesia. The duration of treatment with ONGLYZA until report of tuberculosis ranged from 144 to 929 days. Post-treatment lymphocyte counts were consistently within the reference range for four cases. One patient had lymphopenia prior to initiation of ONGLYZA that remained stable throughout ONGLYZA treatment. The final patient had an isolated lymphocyte count below normal approximately four months prior to the report of tuberculosis. There have been no spontaneous reports of tuberculosis associated with ONGLYZA use. Causality has not been estimated and there are too few cases to date to determine whether tuberculosis is related to ONGLYZA use.

There has been one case of a potential opportunistic infection in the unblinded, controlled clinical trial database to date in an ONGLYZA-treated patient who developed suspected foodborne fatal salmonella sepsis after approximately 600 days of ONGLYZA therapy. There have been no spontaneous reports of opportunistic infections associated with ONGLYZA use.

Vital Signs

No clinically meaningful changes in vital signs have been observed in patients treated with ONGLYZA.

Laboratory Tests

Absolute Lymphocyte Counts

There was a dose-related mean decrease in absolute lymphocyte count observed with ONGLYZA. From a baseline mean absolute lymphocyte count of approximately 2200 cells/microL, mean decreases of approximately 100 and 120 cells/microL with ONGLYZA 5 mg and 10 mg, respectively, relative to placebo were observed at 24 weeks in a pooled analysis of five placebo-controlled clinical studies. Similar effects were observed when ONGLYZA 5 mg was given in initial combination with metformin compared to metformin alone. There was no difference observed for ONGLYZA 2.5 mg relative to placebo. The proportion of patients who were reported to have a lymphocyte count ≤750 cells/microL was 0.5%, 1.5%, 1.4%, and 0.4% in the ONGLYZA 2.5 mg, 5 mg, 10 mg, and placebo groups, respectively. In most patients, recurrence was not observed with repeated exposure to ONGLYZA although some patients had recurrent decreases upon rechallenge that led to discontinuation of ONGLYZA. The decreases in lymphocyte count were not associated with clinically relevant adverse reactions. The 10 mg dosage is not an approved dosage.

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In the SAVOR trial mean decreases of approximately 84 cells/microL with ONGLYZA relative to placebo was observed. The proportion of patients who experienced a decrease in lymphocyte counts to a count of ≤750 cells/microL was 1.6% (136/8280) and 1.0% (78/8212) on ONGLYZA and placebo respectively.

The clinical significance of this decrease in lymphocyte count relative to placebo is not known. When clinically indicated, such as in settings of unusual or prolonged infection, lymphocyte count should be measured. The effect of ONGLYZA on lymphocyte counts in patients with lymphocyte abnormalities (e.g., human immunodeficiency virus) is unknown.

6.2 Postmarketing Experience

Additional adverse reactions have been identified during post-approval use of ONGLYZA. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Hypersensitivity reactions including anaphylaxis, angioedema, and exfoliative skin conditions [*see Contraindications (4)* and *Warnings and Precautions (5.4)*].
- Acute pancreatitis [*see Warnings and Precautions (5.1)*].
- Severe and disabling arthralgia [*see Warnings and Precautions (5.5)*].
- Bullous pemphigoid [see *Warnings and Precautions (5.6)*]

7 DRUG INTERACTIONS

7.1 Strong Inhibitors of CYP3A4/5 Enzymes

Ketoconazole significantly increased saxagliptin exposure. Similar significant increases in plasma concentrations of saxagliptin are anticipated with other strong CYP3A4/5 inhibitors (e.g., atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin). The dose of ONGLYZA should be limited to 2.5 mg when coadministered with a strong CYP3A4/5 inhibitor [*see Dosage and Administration (2.3)* and *Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ONGLYZA, like other antidiabetic medications, should be used during pregnancy only if clearly needed.

Saxagliptin was not teratogenic at any dose tested when administered to pregnant rats and rabbits during periods of organogenesis. Incomplete ossification of the pelvis, a form of developmental delay, occurred in rats at a dose of 240 mg/kg, or approximately 1503 and 66 times human exposure to saxagliptin and the active metabolite, respectively, at the maximum recommended human dose (MRHD) of 5 mg. Maternal toxicity and reduced fetal body weights were observed at 7986 and 328 times the human exposure at the MRHD for saxagliptin and the active metabolite, respectively. Minor skeletal variations in rabbits occurred at a maternally toxic dose of 200 mg/kg, or approximately 1432 and 992 times the MRHD.

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Coadministration of saxagliptin and metformin, to pregnant rats and rabbits during the period of organogenesis, was neither embryolethal nor teratogenic in either species when tested at doses yielding systemic exposures (AUC) up to 100 and 10 times the MRHD (saxagliptin 5 mg and metformin 2000 mg), respectively, in rats; and 249 and 1.1 times the MRHDs in rabbits. In rats, minor developmental toxicity was limited to an increased incidence of wavy ribs; associated maternal toxicity was limited to weight decrements of 11% to 17% over the course of the study, and related reductions in maternal food consumption. In rabbits, coadministration was poorly tolerated in a subset of mothers (12 of 30), resulting in death, moribundity, or abortion. However, among surviving mothers with evaluable litters, maternal toxicity was limited to marginal reductions in body weight over the course of gestation days 21 to 29; and associated developmental toxicity in these litters was limited to fetal body weight decrements of 7%, and a low incidence of delayed ossification of the fetal hyoid.

Saxagliptin administered to female rats from gestation day 6 to lactation day 20 resulted in decreased body weights in male and female offspring only at maternally toxic doses (exposures ≥1629 and 53 times saxagliptin and its active metabolite at the MRHD). No functional or behavioral toxicity was observed in offspring of rats administered saxagliptin at any dose.

Saxagliptin crosses the placenta into the fetus following dosing in pregnant rats.

8.3 Nursing Mothers

Saxagliptin is secreted in the milk of lactating rats at approximately a 1:1 ratio with plasma drug concentrations. It is not known whether saxagliptin is secreted in human milk. Because many drugs are secreted in human milk, caution should be exercised when ONGLYZA is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of ONGLYZA in pediatric patients under 18 years of age have not been established. Additionally, studies characterizing the pharmacokinetics of ONGLYZA in pediatric patients have not been performed.

8.5 Geriatric Use

In the seven, double-blind, controlled clinical safety and efficacy trials of ONGLYZA, a total of 4751 (42.0%) of the 11301 patients randomized to ONGLYZA were 65 years and over, and 1210 (10.7%) were 75 years and over. No overall differences in safety or effectiveness were observed between subjects ≥65 years old and younger subjects. While this clinical experience has not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.

Saxagliptin and its active metabolite are eliminated in part by the kidney. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in the elderly based on renal function [*see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)*].

8.6 Renal Impairment

In a 12-week randomized placebo-controlled trial, ONGLYZA 2.5 mg was administered to 85 subjects with moderate (n=48) or severe (n=18) renal impairment or end-stage renal disease (ESRD) (n=19) [*see Clinical Studies (14)*]. The incidence of adverse events, including serious adverse events and discontinuations due to adverse events, was similar between ONGLYZA and placebo. The overall incidence of reported hypoglycemia was 20% among subjects treated with ONGLYZA 2.5 mg and 22% among subjects treated with placebo. Four ONGLYZA-treated subjects (4.7%) and three placebo-treated subjects (3.5%) reported at least one episode of confirmed symptomatic hypoglycemia (accompanying fingerstick glucose ≤50 mg/dL).

10 OVERDOSAGE

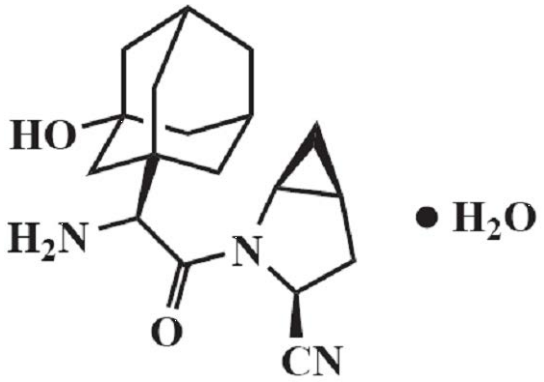
In a controlled clinical trial, once-daily, orally-administered ONGLYZA in healthy subjects at doses up to 400 mg daily for 2 weeks (80 times the MRHD) had no dose-related clinical adverse reactions and no clinically meaningful effect on QTc interval or heart rate.

In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status. Saxagliptin and its active metabolite are removed by hemodialysis (23% of dose over 4 hours).

11 DESCRIPTION

Saxagliptin is an orally-active inhibitor of the DPP4 enzyme.

Saxagliptin monohydrate is described chemically as (1*S*,3*S*,5*S*)-2-[(2*S*)-2-Amino-2-(3-hydroxytricyclo[3.3.1.1^{3,7}]dec-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile, monohydrate or (1*S*,3*S*,5*S*)-2-[(2*S*)-2-Amino-2-(3-hydroxyadamantan-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile hydrate. The empirical formula is $C_{18}H_{25}N_3O_2 \bullet H_2O$ and the molecular weight is 333.43. The structural formula is:



Saxagliptin monohydrate is a white to light yellow or light brown, non-hygroscopic, crystalline powder. It is sparingly soluble in water at 24°C ± 3°C, slightly soluble in ethyl acetate, and soluble in methanol, ethanol, isopropyl alcohol, acetonitrile, acetone, and polyethylene glycol 400 (PEG 400).

Each film-coated tablet of ONGLYZA for oral use contains either 2.79 mg saxagliptin hydrochloride (anhydrous) equivalent to 2.5 mg saxagliptin or 5.58 mg saxagliptin hydrochloride (anhydrous) equivalent to 5 mg saxagliptin and the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, and iron oxides.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Increased concentrations of the incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are released into the bloodstream from the small intestine in response to meals. These hormones cause insulin release from the pancreatic beta cells in a glucose-dependent manner but are inactivated by the DPP4 enzyme within minutes. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, reducing hepatic glucose production. In patients with type 2 diabetes, concentrations of GLP-1 are reduced but the insulin response to GLP-1 is preserved. Saxagliptin is a competitive DPP4 inhibitor that slows the inactivation of the incretin hormones,

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thereby increasing their bloodstream concentrations and reducing fasting and postprandial glucose concentrations in a glucose-dependent manner in patients with type 2 diabetes mellitus.

12.2 Pharmacodynamics

In patients with type 2 diabetes mellitus, administration of ONGLYZA inhibits DPP4 enzyme activity for a 24-hour period. After an oral glucose load or a meal, this DPP4 inhibition resulted in a 2- to 3-fold increase in circulating levels of active GLP-1 and GIP, decreased glucagon concentrations, and increased glucose-dependent insulin secretion from pancreatic beta cells. The rise in insulin and decrease in glucagon were associated with lower fasting glucose concentrations and reduced glucose excursion following an oral glucose load or a meal.

Cardiac Electrophysiology

In a randomized, double-blind, placebo-controlled, 4-way crossover, active comparator study using moxifloxacin in 40 healthy subjects, ONGLYZA was not associated with clinically meaningful prolongation of the QTc interval or heart rate at daily doses up to 40 mg (8 times the MRHD).

12.3 Pharmacokinetics

The pharmacokinetics of saxagliptin and its active metabolite, 5-hydroxy saxagliptin were similar in healthy subjects and in patients with type 2 diabetes mellitus. The C_{max} and AUC values of saxagliptin and its active metabolite increased proportionally in the 2.5 to 400 mg dose range. Following a 5 mg single oral dose of saxagliptin to healthy subjects, the mean plasma AUC values for saxagliptin and its active metabolite were 78 ng•h/mL and 214 ng•h/mL, respectively. The corresponding plasma C_{max} values were 24 ng/mL and 47 ng/mL, respectively. The average variability (%CV) for AUC and C_{max} for both saxagliptin and its active metabolite was less than 25%.

No appreciable accumulation of either saxagliptin or its active metabolite was observed with repeated once-daily dosing at any dose level. No dose- and time-dependence were observed in the clearance of saxagliptin and its active metabolite over 14 days of once-daily dosing with saxagliptin at doses ranging from 2.5 to 400 mg.

Absorption

The median time to maximum concentration (T_{max}) following the 5 mg once daily dose was 2 hours for saxagliptin and 4 hours for its active metabolite. Administration with a high-fat meal resulted in an increase in T_{max} of saxagliptin by approximately 20 minutes as compared to fasted conditions. There was a 27% increase in the AUC of saxagliptin when given with a meal as compared to fasted conditions. ONGLYZA may be administered with or without food.

Distribution

The *in vitro* protein binding of saxagliptin and its active metabolite in human serum is negligible. Therefore, changes in blood protein levels in various disease states (e.g., renal or hepatic impairment) are not expected to alter the disposition of saxagliptin.

Metabolism

The metabolism of saxagliptin is primarily mediated by cytochrome P450 3A4/5 (CYP3A4/5). The major metabolite of saxagliptin is also a DPP4 inhibitor, which is one-half as potent as saxagliptin. Therefore, strong CYP3A4/5 inhibitors and inducers will alter the pharmacokinetics of saxagliptin and its active metabolite [*see Drug Interactions (7.1)*].

Excretion

Saxagliptin is eliminated by both renal and hepatic pathways. Following a single 50 mg dose of ^{14}C-saxagliptin, 24%, 36%, and 75% of the dose was excreted in the urine as saxagliptin, its active metabolite, and total radioactivity, respectively. The average renal clearance of saxagliptin (~230 mL/min) was greater than the average estimated glomerular

filtration rate (~120 mL/min), suggesting some active renal excretion. A total of 22% of the administered radioactivity was recovered in feces representing the fraction of the saxagliptin dose excreted in bile and/or unabsorbed drug from the gastrointestinal tract. Following a single oral dose of ONGLYZA 5 mg to healthy subjects, the mean plasma terminal half-life ($t_{1/2}$) for saxagliptin and its active metabolite was 2.5 and 3.1 hours, respectively.

Specific Populations

Renal Impairment

A single-dose, open-label study was conducted to evaluate the pharmacokinetics of saxagliptin (10 mg dose) in subjects with varying degrees of chronic renal impairment (N=8 per group) compared to subjects with normal renal function. The 10 mg dosage is not an approved dosage. The study included patients with renal impairment classified on the basis of creatinine clearance as mild (>50 to ≤80 mL/min), moderate (30 to ≤50 mL/min), and severe (<30 mL/min), as well as patients with end-stage renal disease on hemodialysis. Creatinine clearance was estimated from serum creatinine based on the Cockcroft-Gault formula:

$$\text{CrCl} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{[72 \times \text{serum creatinine (mg/dL)}]} \{\times 0.85 \text{ for female patients}\}$$

The degree of renal impairment did not affect the C_{max} of saxagliptin or its active metabolite. In subjects with mild renal impairment, the AUC values of saxagliptin and its active metabolite were 20% and 70% higher, respectively, than AUC values in subjects with normal renal function. Because increases of this magnitude are not considered to be clinically relevant, dosage adjustment in patients with mild renal impairment is not recommended. In subjects with moderate or severe renal impairment, the AUC values of saxagliptin and its active metabolite were up to 2.1- and 4.5-fold higher, respectively, than AUC values in subjects with normal renal function. To achieve plasma exposures of saxagliptin and its active metabolite similar to those in patients with normal renal function, the recommended dose is 2.5 mg once daily in patients with moderate and severe renal impairment, as well as in patients with end-stage renal disease requiring hemodialysis. Saxagliptin is removed by hemodialysis.

Hepatic Impairment

In subjects with hepatic impairment (Child-Pugh classes A, B, and C), mean C_{max} and AUC of saxagliptin were up to 8% and 77% higher, respectively, compared to healthy matched controls following administration of a single 10 mg dose of saxagliptin. The 10 mg dosage is not an approved dosage. The corresponding C_{max} and AUC of the active metabolite were up to 59% and 33% lower, respectively, compared to healthy matched controls. These differences are not considered to be clinically meaningful. No dosage adjustment is recommended for patients with hepatic impairment.

Body Mass Index

No dosage adjustment is recommended based on body mass index (BMI) which was not identified as a significant covariate on the apparent clearance of saxagliptin or its active metabolite in the population pharmacokinetic analysis.

Gender

No dosage adjustment is recommended based on gender. There were no differences observed in saxagliptin pharmacokinetics between males and females. Compared to males, females had approximately 25% higher exposure values for the active metabolite than males, but this difference is unlikely to be of clinical relevance. Gender was not identified as a significant covariate on the apparent clearance of saxagliptin and its active metabolite in the population pharmacokinetic analysis.

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Geriatric

No dosage adjustment is recommended based on age alone. Elderly subjects (65-80 years) had 23% and 59% higher geometric mean C_{max} and geometric mean AUC values, respectively, for saxagliptin than young subjects (18-40 years). Differences in active metabolite pharmacokinetics between elderly and young subjects generally reflected the differences observed in saxagliptin pharmacokinetics. The difference between the pharmacokinetics of saxagliptin and the active metabolite in young and elderly subjects is likely due to multiple factors including declining renal function and metabolic capacity with increasing age. Age was not identified as a significant covariate on the apparent clearance of saxagliptin and its active metabolite in the population pharmacokinetic analysis.

Race and Ethnicity

No dosage adjustment is recommended based on race. The population pharmacokinetic analysis compared the pharmacokinetics of saxagliptin and its active metabolite in 309 Caucasian subjects with 105 non-Caucasian subjects (consisting of six racial groups). No significant difference in the pharmacokinetics of saxagliptin and its active metabolite were detected between these two populations.

Drug Interaction Studies

In Vitro Assessment of Drug Interactions

The metabolism of saxagliptin is primarily mediated by CYP3A4/5.

In *in vitro* studies, saxagliptin and its active metabolite did not inhibit CYP1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A4, or induce CYP1A2, 2B6, 2C9, or 3A4. Therefore, saxagliptin is not expected to alter the metabolic clearance of coadministered drugs that are metabolized by these enzymes. Saxagliptin is a P-glycoprotein (P-gp) substrate but is not a significant inhibitor or inducer of P-gp.

In Vivo Assessment of Drug Interactions

Table 2: Effect of Coadministered Drugs on Systemic Exposures of Saxagliptin and its Active Metabolite, 5-hydroxy Saxagliptin

Coadministered Drug	**Dosage of Coadministered Drug***	**Dosage of Saxagliptin***	**Geometric Mean Ratio (ratio with/without coadministered drug) No Effect = 1.00**		
				AUC†	**C_{max}**
No dosing adjustments required for the following:					
Metformin	1000 mg	100 mg	saxagliptin 5-hydroxy saxagliptin	0.98 0.99	0.79 0.88
Glyburide	5 mg	10 mg	saxagliptin 5-hydroxy saxagliptin	0.98 ND	1.08 ND
Pioglitazone‡	45 mg QD for 10 days	10 mg QD for 5 days	saxagliptin 5-hydroxy saxagliptin	1.11 ND	1.11 ND
Digoxin	0.25 mg q6h first day followed by q12h second day followed by QD for 5 days	10 mg QD for 7 days	saxagliptin 5-hydroxy saxagliptin	1.05 1.06	0.99 1.02
Simvastatin	40 mg QD for 8 days	10 mg QD for 4 days	saxagliptin 5-hydroxy saxagliptin	1.12 1.02	1.21 1.08
Diltiazem	360 mg LA QD for 9 days	10 mg	saxagliptin	2.09	1.63

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Coadministered Drug	Dosage of Coadministered Drug*	Dosage of Saxagliptin*	Geometric Mean Ratio (ratio with/without coadministered drug) No Effect = 1.00		
				AUC†	C_{max}
			5-hydroxy saxagliptin	0.66	0.57
Rifampin§	600 mg QD for 6 days	5 mg	saxagliptin 5-hydroxy saxagliptin	0.24 1.03	0.47 1.39
Omeprazole	40 mg QD for 5 days	10 mg	saxagliptin 5-hydroxy saxagliptin	1.13 ND	0.98 ND
Aluminum hydroxide + magnesium hydroxide + simethicone	aluminum hydroxide: 2400 mg magnesium hydroxide: 2400 mg simethicone: 240 mg	10 mg	saxagliptin 5-hydroxy saxagliptin	0.97 ND	0.74 ND
Famotidine	40 mg	10 mg	saxagliptin 5-hydroxy saxagliptin	1.03 ND	1.14 ND
Limit ONGLYZA dose to 2.5 mg once daily when coadministered with strong CYP3A4/5 inhibitors [*see* *Drug Interactions (7.1)* and *Dosage and Administration (2.3)*]:					
Ketoconazole	200 mg BID for 9 days	100 mg	saxagliptin 5-hydroxy saxagliptin	2.45 0.12	1.62 0.05
Ketoconazole	200 mg BID for 7 days	20 mg	saxagliptin 5-hydroxy saxagliptin	3.67 ND	2.44 ND

* Single dose unless otherwise noted. The 10 mg saxagliptin dose is not an approved dosage.
† AUC = AUC(INF) for drugs given as single dose and AUC = AUC(TAU) for drugs given in multiple doses
‡ Results exclude one subject
§ The plasma dipeptidyl peptidase-4 (DPP4) activity inhibition over a 24-hour dose interval was not affected by rifampin
ND=not determined; QD=once daily; q6h=every 6 hours; q12h=every 12 hours; BID=twice daily; LA=long acting

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Table 3: Effect of Saxagliptin on Systemic Exposures of Coadministered Drugs

Coadministered Drug	Dosage of Coadministered Drug*	Dosage of Saxagliptin*	Geometric Mean Ratio (ratio with/without saxagliptin) No Effect = 1.00		
				AUC†	C_{max}
No dosing adjustments required for the following:					
Metformin	1000 mg	100 mg	metformin	1.20	1.09
Glyburide	5 mg	10 mg	glyburide	1.06	1.16
Pioglitazone‡	45 mg QD for 10 days	10 mg QD for 5 days	pioglitazone hydroxy-pioglitazone	1.08 ND	1.14 ND
Digoxin	0.25 mg q6h first day followed by q12h second day followed by QD for 5 days	10 mg QD for 7 days	digoxin	1.06	1.09
Simvastatin	40 mg QD for 8 days	10 mg QD for 4 days	simvastatin simvastatin acid	1.04 1.16	0.88 1.00
Diltiazem	360 mg LA QD for 9 days	10 mg	diltiazem	1.10	1.16
Ketoconazole	200 mg BID for 9 days	100 mg	ketoconazole	0.87	0.84
Ethinyl estradiol and Norgestimate	ethinyl estradiol 0.035 mg and norgestimate 0.250 mg for 21 days	5 mg QD for 21 days	ethinyl estradiol norelgestromin norgestrel	1.07 1.10 1.13	0.98 1.09 1.17

* Single dose unless otherwise noted. The 10 mg and 100 mg saxagliptin doses are not approved dosages.
† AUC = AUC(INF) for drugs given as single dose and AUC = AUC(TAU) for drugs given in multiple doses
‡ Results include all subjects
ND=not determined; QD=once daily; q6h=every 6 hours; q12h=every 12 hours; BID=twice daily; LA=long acting

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Saxagliptin did not induce tumors in either mice (50, 250, and 600 mg/kg) or rats (25, 75, 150, and 300 mg/kg) at the highest doses evaluated. The highest doses evaluated in mice were equivalent to approximately 870 (males) and 1165 (females) times the human exposure at the MRHD of 5 mg/day. In rats, exposures were approximately 355 (males) and 2217 (females) times the MRHD.

Mutagenesis

Saxagliptin was not mutagenic or clastogenic with or without metabolic activation in an *in vitro* Ames bacterial assay, an *in vitro* cytogenetics assay in primary human lymphocytes, an *in vivo* oral micronucleus assay in rats, an *in vivo* oral DNA repair study in rats, and an oral *in vivo/in vitro* cytogenetics study in rat peripheral blood lymphocytes. The active metabolite was not mutagenic in an *in vitro* Ames bacterial assay.

Impairment of Fertility

In a rat fertility study, males were treated with oral gavage doses for 2 weeks prior to mating, during mating, and up to scheduled termination (approximately 4 weeks total) and females were treated with oral gavage doses for 2 weeks prior to

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mating through gestation day 7. No adverse effects on fertility were observed at exposures of approximately 603 (males) and 776 (females) times the MRHD. Higher doses that elicited maternal toxicity also increased fetal resorptions (approximately 2069 and 6138 times the MRHD). Additional effects on estrous cycling, fertility, ovulation, and implantation were observed at approximately 6138 times the MRHD.

13.2 Animal Toxicology and/or Pharmacology

Saxagliptin produced adverse skin changes in the extremities of cynomolgus monkeys (scabs and/or ulceration of tail, digits, scrotum, and/or nose). Skin lesions were reversible at ≥20 times the MRHD but in some cases were irreversible and necrotizing at higher exposures. Adverse skin changes were not observed at exposures similar to (1 to 3 times) the MRHD of 5 mg. Clinical correlates to skin lesions in monkeys have not been observed in human clinical trials of saxagliptin.

14 CLINICAL STUDIES

14.1 Glycemic Efficacy Trials

ONGLYZA has been studied as monotherapy and in combination with metformin, glyburide, and thiazolidinedione (pioglitazone and rosiglitazone) therapy.

A total of 4148 patients with type 2 diabetes mellitus were randomized in six, double-blind, controlled clinical trials conducted to evaluate the safety and glycemic efficacy of ONGLYZA. A total of 3021 patients in these trials were treated with ONGLYZA. In these trials, the mean age was 54 years, and 71% of patients were Caucasian, 16% were Asian, 4% were black, and 9% were of other racial groups. An additional 423 patients, including 315 who received ONGLYZA, participated in a placebo-controlled, dose-ranging study of 6 to 12 weeks in duration.

In these six, double-blind trials, ONGLYZA was evaluated at doses of 2.5 mg and 5 mg once daily. Three of these trials also evaluated an ONGLYZA dose of 10 mg daily. The 10 mg daily dose of ONGLYZA did not provide greater efficacy than the 5 mg daily dose. The 10 mg dosage is not an approved dosage. Treatment with ONGLYZA 5 mg and 2.5 mg doses produced clinically relevant and statistically significant improvements in A1C, fasting plasma glucose (FPG), and 2-hour postprandial glucose (PPG) following a standard oral glucose tolerance test (OGTT), compared to control. Reductions in A1C were seen across subgroups including gender, age, race, and baseline BMI.

ONGLYZA was not associated with significant changes from baseline in body weight or fasting serum lipids compared to placebo.

ONGLYZA has also been evaluated in four additional trials in patients with type 2 diabetes: an active-controlled trial comparing add-on therapy with ONGLYZA to glipizide in 858 patients inadequately controlled on metformin alone, a trial comparing ONGLYZA to placebo in 455 patients inadequately controlled on insulin alone or on insulin in combination with metformin, a trial comparing ONGLYZA to placebo in 257 patients inadequately controlled on metformin plus a sulfonylurea, and a trial comparing ONGLYZA to placebo in 170 patients with type 2 diabetes and moderate or severe renal impairment or ESRD.

Monotherapy

A total of 766 patients with type 2 diabetes inadequately controlled on diet and exercise (A1C ≥7% to ≤10%) participated in two 24-week, double-blind, placebo-controlled trials evaluating the efficacy and safety of ONGLYZA monotherapy.

In the first trial, following a 2-week single-blind diet, exercise, and placebo lead-in period, 401 patients were randomized to 2.5 mg, 5 mg, or 10 mg of ONGLYZA or placebo. The 10 mg dosage is not an approved dosage. Patients who failed to meet specific glycemic goals during the study were treated with metformin rescue therapy, added on to placebo or

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ONGLYZA. Efficacy was evaluated at the last measurement prior to rescue therapy for patients needing rescue. Dose titration of ONGLYZA was not permitted.

Treatment with ONGLYZA 2.5 mg and 5 mg daily provided significant improvements in A1C, FPG, and PPG compared to placebo (Table 4). The percentage of patients who discontinued for lack of glycemic control or who were rescued for meeting prespecified glycemic criteria was 16% in the ONGLYZA 2.5 mg treatment group, 20% in the ONGLYZA 5 mg treatment group, and 26% in the placebo group).

Table 4: Glycemic Parameters at Week 24 in a Placebo-Controlled Study of ONGLYZA Monotherapy in Patients with Type 2 Diabetes*

Efficacy Parameter	**ONGLYZA 2.5 mg N=102**	**ONGLYZA 5 mg N=106**	**Placebo N=95**
Hemoglobin A1C (%)	**N=100**	**N=103**	**N=92**
Baseline (mean)	7.9	8.0	7.9
Change from baseline (adjusted mean†)	−0.4	−0.5	+0.2
Difference from placebo (adjusted mean†)	−0.6‡	−0.6‡	
95% Confidence Interval	(−0.9, −0.3)	(−0.9, −0.4)	
Percent of patients achieving A1C <7%	35% (35/100)	38%§ (39/103)	24% (22/92)
Fasting Plasma Glucose (mg/dL)	**N=101**	**N=105**	**N=92**
Baseline (mean)	178	171	172
Change from baseline (adjusted mean†)	−15	−9	+6
Difference from placebo (adjusted mean†)	−21§	−15§	
95% Confidence Interval	(−31, −10)	(−25, −4)	
2-hour Postprandial Glucose (mg/dL)	**N=78**	**N=84**	**N=71**
Baseline (mean)	279	278	283
Change from baseline (adjusted mean†)	−45	−43	−6
Difference from placebo (adjusted mean†)	−39¶	−37§	
95% Confidence Interval	(−61, −16)	(−59, −15)	

* Intent-to-treat population using last observation on study or last observation prior to metformin rescue therapy for patients needing rescue
† Least squares mean adjusted for baseline value
‡ p-value <0.0001 compared to placebo
§ p-value <0.05 compared to placebo
¶ Significance was not tested for the 2-hour PPG for the 2.5 mg dose of ONGLYZA

A second 24-week monotherapy trial was conducted to assess a range of dosing regimens for ONGLYZA. Treatment-naive patients with inadequately controlled diabetes (A1C ≥7% to ≤10%) underwent a 2-week, single-blind diet, exercise, and placebo lead-in period. A total of 365 patients were randomized to 2.5 mg every morning, 5 mg every morning, 2.5 mg with possible titration to 5 mg every morning, or 5 mg every evening of ONGLYZA, or placebo. Patients who failed to meet specific glycemic goals during the study were treated with metformin rescue therapy added on to placebo or ONGLYZA; the number of patients randomized per treatment group ranged from 71 to 74.

Treatment with either ONGLYZA 5 mg every morning or 5 mg every evening provided significant improvements in A1C versus placebo (mean placebo-corrected reductions of –0.4% and –0.3%, respectively). Treatment with ONGLYZA 2.5 mg every morning also provided significant improvement in A1C versus placebo (mean placebo-corrected reduction of –0.4%).

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Combination Therapy

Add-On Combination Therapy with Metformin

A total of 743 patients with type 2 diabetes participated in this 24-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of ONGLYZA in combination with metformin in patients with inadequate glycemic control (A1C ≥7% and ≤10%) on metformin alone. To qualify for enrollment, patients were required to be on a stable dose of metformin (1500-2550 mg daily) for at least 8 weeks.

Patients who met eligibility criteria were enrolled in a single-blind, 2-week, dietary and exercise placebo lead-in period during which patients received metformin at their pre-study dose, up to 2500 mg daily. Following the lead-in period, eligible patients were randomized to 2.5 mg, 5 mg, or 10 mg of ONGLYZA or placebo in addition to their current dose of open-label metformin. The 10 mg dosage is not an approved dosage. Patients who failed to meet specific glycemic goals during the study were treated with pioglitazone rescue therapy, added on to existing study medications. Dose titrations of ONGLYZA and metformin were not permitted.

ONGLYZA 2.5 mg and 5 mg add-on to metformin provided significant improvements in A1C, FPG, and PPG compared with placebo add-on to metformin (Table 5). Mean changes from baseline for A1C over time and at endpoint are shown in Figure 1. The proportion of patients who discontinued for lack of glycemic control or who were rescued for meeting prespecified glycemic criteria was 15% in the ONGLYZA 2.5 mg add-on to metformin group, 13% in the ONGLYZA 5 mg add-on to metformin group, and 27% in the placebo add-on to metformin group.

Table 5: Glycemic Parameters at Week 24 in a Placebo-Controlled Study of ONGLYZA as Add-On Combination Therapy with Metformin*

Efficacy Parameter	**ONGLYZA 2.5 mg + Metformin N=192**	**ONGLYZA 5 mg + Metformin N=191**	**Placebo + Metformin N=179**
Hemoglobin A1C (%)	**N=186**	**N=186**	**N=175**
Baseline (mean)	8.1	8.1	8.1
Change from baseline (adjusted mean†)	−0.6	−0.7	+0.1
Difference from placebo (adjusted mean†)	−0.7‡	−0.8‡	
95% Confidence Interval	(−0.9, −0.5)	(−1.0, −0.6)	
Percent of patients achieving A1C <7%	37%§ (69/186)	44%§ (81/186)	17% (29/175)
Fasting Plasma Glucose (mg/dL)	**N=188**	**N=187**	**N=176**
Baseline (mean)	174	179	175
Change from baseline (adjusted mean†)	−14	−22	+1
Difference from placebo (adjusted mean†)	−16§	−23§	
95% Confidence Interval	(−23, −9)	(−30, −16)	
2-hour Postprandial Glucose (mg/dL)	**N=155**	**N=155**	**N=135**
Baseline (mean)	294	296	295
Change from baseline (adjusted mean†)	−62	−58	−18
Difference from placebo (adjusted mean†)	−44§	−40§	
95% Confidence Interval	(−60, −27)	(−56, −24)	

* Intent-to-treat population using last observation on study or last observation prior to pioglitazone rescue therapy for patients needing rescue
† Least squares mean adjusted for baseline value
‡ p-value <0.0001 compared to placebo + metformin
§ p-value <0.05 compared to placebo + metformin

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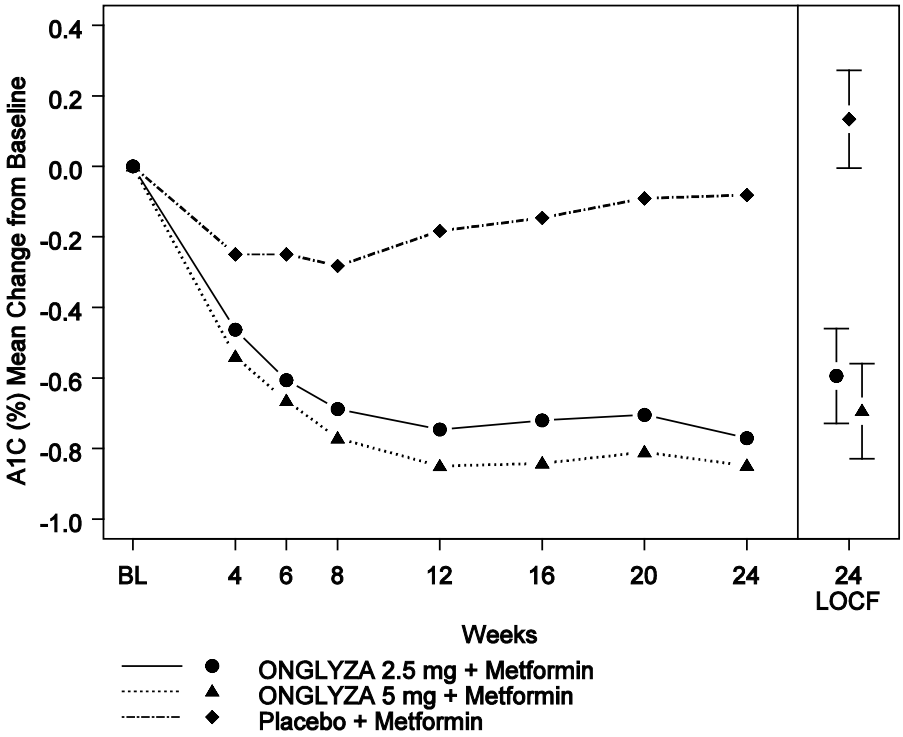
Figure 1: Mean Change from Baseline in A1C in a Placebo-Controlled Trial of ONGLYZA as Add-On Combination Therapy with Metformin*



* Includes patients with a baseline and week 24 value.
Week 24 (LOCF) includes intent-to-treat population using last observation on study prior to pioglitazone rescue therapy for patients needing rescue. Mean change from baseline is adjusted for baseline value.

Add-On Combination Therapy with a Thiazolidinedione

A total of 565 patients with type 2 diabetes participated in this 24-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of ONGLYZA in combination with a thiazolidinedione (TZD) in patients with inadequate glycemic control (A1C ≥7% to ≤10.5%) on TZD alone. To qualify for enrollment, patients were required to be on a stable dose of pioglitazone (30-45 mg once daily) or rosiglitazone (4 mg once daily or 8 mg either once daily or in two divided doses of 4 mg) for at least 12 weeks.

Patients who met eligibility criteria were enrolled in a single-blind, 2-week, dietary and exercise placebo lead-in period during which patients received TZD at their pre-study dose. Following the lead-in period, eligible patients were randomized to 2.5 mg or 5 mg of ONGLYZA or placebo in addition to their current dose of TZD. Patients who failed to meet specific glycemic goals during the study were treated with metformin rescue, added on to existing study medications. Dose titration of ONGLYZA or TZD was not permitted during the study. A change in TZD regimen from rosiglitazone to pioglitazone at specified, equivalent therapeutic doses was permitted at the investigator’s discretion if believed to be medically appropriate.

ONGLYZA 2.5 mg and 5 mg add-on to TZD provided significant improvements in A1C, FPG, and PPG compared with placebo add-on to TZD (Table 6). The proportion of patients who discontinued for lack of glycemic control or who were rescued for meeting prespecified glycemic criteria was 10% in the ONGLYZA 2.5 mg add-on to TZD group, 6% for the ONGLYZA 5 mg add-on to TZD group, and 10% in the placebo add-on to TZD group.

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Table 6: Glycemic Parameters at Week 24 in a Placebo-Controlled Study of ONGLYZA as Add-On Combination Therapy with a Thiazolidinedione*

Efficacy Parameter	ONGLYZA 2.5 mg + TZD N=195	ONGLYZA 5 mg + TZD N=186	Placebo + TZD N=184
Hemoglobin A1C (%)	**N=192**	**N=183**	**N=180**
Baseline (mean)	8.3	8.4	8.2
Change from baseline (adjusted mean[†])	−0.7	−0.9	−0.3
Difference from placebo (adjusted mean[†])	−0.4[§]	−0.6[‡]	
95% Confidence Interval	(−0.6, −0.2)	(−0.8, −0.4)	
Percent of patients achieving A1C <7%	42%[§] (81/192)	42%[§] (77/184)	26% (46/180)
Fasting Plasma Glucose (mg/dL)	**N=193**	**N=185**	**N=181**
Baseline (mean)	163	160	162
Change from baseline (adjusted mean[†])	−14	−17	−3
Difference from placebo (adjusted mean[†])	−12[§]	−15[§]	
95% Confidence Interval	(−20, −3)	(−23, −6)	
2-hour Postprandial Glucose (mg/dL)	**N=156**	**N=134**	**N=127**
Baseline (mean)	296	303	291
Change from baseline (adjusted mean[†])	−55	−65	−15
Difference from placebo (adjusted mean[†])	−40[§]	−50[§]	
95% Confidence Interval	(−56, −24)	(−66, −34)	

* Intent-to-treat population using last observation on study or last observation prior to metformin rescue therapy for patients needing rescue
† Least squares mean adjusted for baseline value
‡ p-value <0.0001 compared to placebo + TZD
§ p-value <0.05 compared to placebo + TZD

Add-On Combination Therapy with Glyburide

A total of 768 patients with type 2 diabetes participated in this 24-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of ONGLYZA in combination with a sulfonylurea (SU) in patients with inadequate glycemic control at enrollment (A1C ≥7.5% to ≤10%) on a submaximal dose of SU alone. To qualify for enrollment, patients were required to be on a submaximal dose of SU for 2 months or greater. In this study, ONGLYZA in combination with a fixed, intermediate dose of SU was compared to titration to a higher dose of SU.

Patients who met eligibility criteria were enrolled in a single-blind, 4-week, dietary and exercise lead-in period, and placed on glyburide 7.5 mg once daily. Following the lead-in period, eligible patients with A1C ≥7% to ≤10% were randomized to either 2.5 mg or 5 mg of ONGLYZA add-on to 7.5 mg glyburide or to placebo plus a 10 mg total daily dose of glyburide. Patients who received placebo were eligible to have glyburide up-titrated to a total daily dose of 15 mg. Up-titration of glyburide was not permitted in patients who received ONGLYZA 2.5 mg or 5 mg. Glyburide could be down-titrated in any treatment group once during the 24-week study period due to hypoglycemia as deemed necessary by the investigator. Approximately 92% of patients in the placebo plus glyburide group were up-titrated to a final total daily dose of 15 mg during the first 4 weeks of the study period. Patients who failed to meet specific glycemic goals during the study were treated with metformin rescue, added on to existing study medication. Dose titration of ONGLYZA was not permitted during the study.

In combination with glyburide, ONGLYZA 2.5 mg and 5 mg provided significant improvements in A1C, FPG, and PPG compared with the placebo plus up-titrated glyburide group (Table 7). The proportion of patients who discontinued for

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lack of glycemic control or who were rescued for meeting prespecified glycemic criteria was 18% in the ONGLYZA 2.5 mg add-on to glyburide group, 17% in the ONGLYZA 5 mg add-on to glyburide group, and 30% in the placebo plus up-titrated glyburide group.

Table 7: Glycemic Parameters at Week 24 in a Placebo-Controlled Study of ONGLYZA as Add-On Combination Therapy with Glyburide*

Efficacy Parameter	**ONGLYZA 2.5 mg + Glyburide 7.5 mg N=248**	**ONGLYZA 5 mg + Glyburide 7.5 mg N=253**	**Placebo + Up-Titrated Glyburide N=267**
Hemoglobin A1C (%)	**N=246**	**N=250**	**N=264**
Baseline (mean)	8.4	8.5	8.4
Change from baseline (adjusted mean[†])	−0.5	−0.6	+0.1
Difference from up-titrated glyburide (adjusted mean[†])	−0.6[‡]	−0.7[‡]	
95% Confidence Interval	(−0.8, −0.5)	(−0.9, −0.6)	
Percent of patients achieving A1C <7%	22%[§] (55/246)	23%[§] (57/250)	9% (24/264)
Fasting Plasma Glucose (mg/dL)	**N=247**	**N=252**	**N=265**
Baseline (mean)	170	175	174
Change from baseline (adjusted mean[†])	−7	−10	+1
Difference from up-titrated glyburide (adjusted mean[†])	−8[§]	−10[§]	
95% Confidence Interval	(−14, −1)	(−17, −4)	
2-hour Postprandial Glucose (mg/dL)	**N=195**	**N=202**	**N=206**
Baseline (mean)	309	315	323
Change from baseline (adjusted mean[†])	−31	−34	+8
Difference from up-titrated glyburide (adjusted mean[†])	−38[§]	−42[§]	
95% Confidence Interval	(−50, −27)	(−53, −31)	

* Intent-to-treat population using last observation on study or last observation prior to metformin rescue therapy for patients needing rescue
† Least squares mean adjusted for baseline value
‡ p-value <0.0001 compared to placebo + up-titrated glyburide
§ p-value <0.05 compared to placebo + up-titrated glyburide

Coadministration with Metformin in Treatment-Naive Patients

A total of 1306 treatment-naive patients with type 2 diabetes mellitus participated in this 24-week, randomized, double-blind, active-controlled trial to evaluate the efficacy and safety of ONGLYZA coadministered with metformin in patients with inadequate glycemic control (A1C ≥8% to ≤12%) on diet and exercise alone. Patients were required to be treatment-naive to be enrolled in this study.

Patients who met eligibility criteria were enrolled in a single-blind, 1-week, dietary and exercise placebo lead-in period. Patients were randomized to one of four treatment arms: ONGLYZA 5 mg + metformin 500 mg, saxagliptin 10 mg + metformin 500 mg, saxagliptin 10 mg + placebo, or metformin 500 mg + placebo. The 10 mg saxagliptin dosage is not an approved dosage. ONGLYZA was dosed once daily. In the 3 treatment groups using metformin, the metformin dose was up-titrated weekly in 500 mg per day increments, as tolerated, to a maximum of 2000 mg per day based on FPG. Patients who failed to meet specific glycemic goals during the studies were treated with pioglitazone rescue as add-on therapy.

Coadministration of ONGLYZA 5 mg plus metformin provided significant improvements in A1C, FPG, and PPG compared with placebo plus metformin (Table 8).

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Table 8: Glycemic Parameters at Week 24 in a Placebo-Controlled Trial of ONGLYZA Coadministration with Metformin in Treatment-Naive Patients*

Efficacy Parameter	ONGLYZA 5 mg + Metformin N=320	Placebo + Metformin N=328
Hemoglobin A1C (%)	**N=306**	**N=313**
Baseline (mean)	9.4	9.4
Change from baseline (adjusted mean[†])	−2.5	−2.0
Difference from placebo + metformin (adjusted mean[†])	−0.5[‡]	
95% Confidence Interval	(−0.7, −0.4)	
Percent of patients achieving A1C <7%	60%[§] (185/307)	41% (129/314)
Fasting Plasma Glucose (mg/dL)	**N=315**	**N=320**
Baseline (mean)	199	199
Change from baseline (adjusted mean[†])	−60	−47
Difference from placebo + metformin (adjusted mean[†])	−13[§]	
95% Confidence Interval	(−19, −6)	
2-hour Postprandial Glucose (mg/dL)	**N=146**	**N=141**
Baseline (mean)	340	355
Change from baseline (adjusted mean[†])	−138	−97
Difference from placebo + metformin (adjusted mean[†])	−41[§]	
95% Confidence Interval	(−57, −25)	

* Intent-to-treat population using last observation on study or last observation prior to pioglitazone rescue therapy for patients needing rescue
† Least squares mean adjusted for baseline value
‡ p-value <0.0001 compared to placebo + metformin
§ p-value <0.05 compared to placebo + metformin

Add-On Combination Therapy with Metformin versus Glipizide Add-On Combination Therapy with Metformin

In this 52-week, active-controlled trial, a total of 858 patients with type 2 diabetes and inadequate glycemic control (A1C >6.5% and ≤10%) on metformin alone were randomized to double-blind add-on therapy with ONGLYZA or glipizide. Patients were required to be on a stable dose of metformin (at least 1500 mg daily) for at least 8 weeks prior to enrollment.

Patients who met eligibility criteria were enrolled in a single-blind, 2-week, dietary and exercise placebo lead-in period during which patients received metformin (1500-3000 mg based on their pre-study dose). Following the lead-in period, eligible patients were randomized to 5 mg of ONGLYZA or 5 mg of glipizide in addition to their current dose of open-label metformin. Patients in the glipizide plus metformin group underwent blinded titration of the glipizide dose during the first 18 weeks of the trial up to a maximum glipizide dose of 20 mg per day. Titration was based on a goal FPG ≤110 mg/dL or the highest tolerable glipizide dose. Fifty percent (50%) of the glipizide-treated patients were titrated to the 20-mg daily dose; 21% of the glipizide-treated patients had a final daily glipizide dose of 5 mg or less. The mean final daily dose of glipizide was 15 mg.

After 52 weeks of treatment, ONGLYZA and glipizide resulted in similar mean reductions from baseline in A1C when added to metformin therapy (Table 9). This conclusion may be limited to patients with baseline A1C comparable to those in the trial (91% of patients had baseline A1C <9%).

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From a baseline mean body weight of 89 kg, there was a statistically significant mean reduction of 1.1 kg in patients treated with ONGLYZA compared to a mean weight gain of 1.1 kg in patients treated with glipizide (p<0.0001).

Table 9: Glycemic Parameters at Week 52 in an Active-Controlled Trial of ONGLYZA versus Glipizide in Combination with Metformin*

Efficacy Parameter	ONGLYZA 5 mg + Metformin N=428	Titrated Glipizide + Metformin N=430
Hemoglobin A1C (%)	**N=423**	**N=423**
Baseline (mean)	7.7	7.6
Change from baseline (adjusted mean[†])	−0.6	−0.7
Difference from glipizide + metformin (adjusted mean[†])	0.1	
95% Confidence Interval	(−0.02, 0.2)[‡]	
Fasting Plasma Glucose (mg/dL)	**N=420**	**N=420**
Baseline (mean)	162	161
Change from baseline (adjusted mean[†])	−9	−16
Difference from glipizide + metformin (adjusted mean[†])	6	
95% Confidence Interval	(2, 11)[§]	

* Intent-to-treat population using last observation on study
† Least squares mean adjusted for baseline value
‡ ONGLYZA + metformin is considered non-inferior to glipizide + metformin because the upper limit of this confidence interval is less than the prespecified non-inferiority margin of 0.35%
§ Significance not tested

Add-On Combination Therapy with Insulin (with or without metformin)

A total of 455 patients with type 2 diabetes participated in this 24-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of ONGLYZA in combination with insulin in patients with inadequate glycemic control (A1C ≥7.5% and ≤11%) on insulin alone (N=141) or on insulin in combination with a stable dose of metformin (N=314). Patients were required to be on a stable dose of insulin (≥30 units to ≤150 units daily) with ≤20% variation in total daily dose for ≥8 weeks prior to screening. Patients entered the trial on intermediate- or long-acting (basal) insulin or premixed insulin. Patients using short-acting insulins were excluded unless the short-acting insulin was administered as part of a premixed insulin.

Patients who met eligibility criteria were enrolled in a single-blind, four-week, dietary and exercise placebo lead-in period during which patients received insulin (and metformin if applicable) at their pretrial dose(s). Following the lead-in period, eligible patients were randomized to add-on therapy with either ONGLYZA 5 mg or placebo. Doses of the antidiabetic therapies were to remain stable but patients were rescued and allowed to adjust the insulin regimen if specific glycemic goals were not met or if the investigator learned that the patient had self-increased the insulin dose by >20%. Data after rescue were excluded from the primary efficacy analyses.

Add-on therapy with ONGLYZA 5 mg provided significant improvements from baseline to Week 24 in A1C and PPG compared with add-on placebo (Table 10). Similar mean reductions in A1C versus placebo were observed for patients using ONGLYZA 5 mg add-on to insulin alone and ONGLYZA 5 mg add-on to insulin in combination with metformin (−0.4% and −0.4%, respectively). The percentage of patients who discontinued for lack of glycemic control or who were rescued was 23% in the ONGLYZA group and 32% in the placebo group.

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The mean daily insulin dose at baseline was 53 units in patients treated with ONGLYZA 5 mg and 55 units in patients treated with placebo. The mean change from baseline in daily dose of insulin was 2 units for the ONGLYZA 5 mg group and 5 units for the placebo group.

Table 10: Glycemic Parameters at Week 24 in a Placebo-Controlled Trial of ONGLYZA as Add-On Combination Therapy with Insulin*

Efficacy Parameter	**ONGLYZA 5 mg + Insulin (+/− Metformin) N=304**	**Placebo + Insulin (+/− Metformin) N=151**
Hemoglobin A1C (%)	**N=300**	**N=149**
Baseline (mean)	8.7	8.7
Change from baseline (adjusted mean[†])	−0.7	−0.3
Difference from placebo (adjusted mean[†])	−0.4[‡]	
95% Confidence Interval	(−0.6, −0.2)	
2-hour Postprandial Glucose (mg/dL)	**N=262**	**N=129**
Baseline (mean)	251	255
Change from baseline (adjusted mean[†])	−27	−4
Difference from placebo (adjusted mean[†])	−23[§]	
95% Confidence Interval	(−37, −9)	

* Intent-to-treat population using last observation on study or last observation prior to insulin rescue therapy for patients needing rescue

† Least squares mean adjusted for baseline value and metformin use at baseline

‡ p-value <0.0001 compared to placebo + insulin

§ p-value <0.05 compared to placebo + insulin

The change in fasting plasma glucose from baseline to Week 24 was also tested, but was not statistically significant. The percent of patients achieving an A1C <7% was 17% (52/300) with ONGLYZA in combination with insulin compared to 7% (10/149) with placebo. Significance was not tested.

Add-On Combination Therapy with Metformin plus Sulfonylurea

A total of 257 patients with type 2 diabetes participated in this 24-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of ONGLYZA in combination with metformin plus a sulfonylurea in patients with inadequate glycemic control (A1C ≥7% and ≤10%). Patients were to be on a stable combined dose of metformin extended-release or immediate-release (at maximum tolerated dose, with minimum dose for enrollment being 1500 mg) and a sulfonylurea (at maximum tolerated dose, with minimum dose for enrollment being ≥50% of the maximum recommended dose) for ≥8 weeks prior to enrollment.

Patients who met eligibility criteria were entered in a 2-week enrollment period to allow assessment of inclusion/exclusion criteria. Following the 2-week enrollment period, eligible patients were randomized to either double-blind ONGLYZA (5 mg once daily) or double-blind matching placebo for 24 weeks. During the 24-week double-blind treatment period, patients were to receive metformin and a sulfonylurea at the same constant dose ascertained during enrollment. Sulfonylurea dose could be down titrated once in the case of a major hypoglycemic event or recurring minor hypoglycemic events. In the absence of hypoglycemia, titration (up or down) of study medication during the treatment period was prohibited.

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ONGLYZA in combination with metformin plus a sulfonylurea provided significant improvements in A1C and PPG compared with placebo in combination with metformin plus a sulfonylurea (Table 11). The percentage of patients who discontinued for lack of glycemic control was 6% in the ONGLYZA group and 5% in the placebo group.

Table 11: Glycemic Parameters at Week 24 in a Placebo-Controlled Trial of ONGLYZA as Add-On Combination Therapy with Metformin plus Sulfonylurea*

Efficacy Parameter	**ONGLYZA 5 mg + Metformin plus Sulfonylurea N=129**	**Placebo + Metformin plus Sulfonylurea N=128**
Hemoglobin A1C (%)	**N=127**	**N=127**
Baseline (mean)	8.4	8.2
Change from baseline (adjusted mean[†])	−0.7	−0.1
Difference from placebo (adjusted mean[†])	−0.7[‡]	
95% Confidence Interval	(−0.9, −0.5)	
2-hour Postprandial Glucose (mg/dL)	**N=115**	**N=113**
Baseline (mean)	268	262
Change from baseline (adjusted mean[†])	−12	5
Difference from placebo (adjusted mean[†])	−17[§]	
95% Confidence Interval	(−32, −2)	

* Intent-to-treat population using last observation prior to discontinuation

† Least squares mean adjusted for baseline value

‡ p-value <0.0001 compared to placebo + metformin plus sulfonylurea

§ p-value <0.05 compared to placebo + metformin plus sulfonylurea

The change in fasting plasma glucose from baseline to Week 24 was also tested, but was not statistically significant. The percent of patients achieving an A1C <7% was 31% (39/127) with ONGLYZA in combination with metformin plus a sulfonylurea compared to 9% (12/127) with placebo. Significance was not tested.

14.2 Renal Impairment

A total of 170 patients participated in a 12-week, randomized, double-blind, placebo-controlled trial conducted to evaluate the efficacy and safety of ONGLYZA 2.5 mg once daily compared with placebo in patients with type 2 diabetes and moderate (n=90) or severe (n=41) renal impairment or ESRD (n=39). In this trial, 98% of the patients were using background antidiabetic medications (75% were using insulin and 31% were using oral antidiabetic medications, mostly sulfonylureas).

After 12 weeks of treatment, ONGLYZA 2.5 mg provided significant improvement in A1C compared to placebo (Table 12). In the subgroup of patients with ESRD, ONGLYZA and placebo resulted in comparable reductions in A1C from baseline to Week 12. This finding is inconclusive because the trial was not adequately powered to show efficacy within specific subgroups of renal impairment.

After 12 weeks of treatment, the mean change in FPG was −12 mg/dL with ONGLYZA 2.5 mg and −13 mg/dL with placebo. Compared to placebo, the mean change in FPG with ONGLYZA was −12 mg/dL in the subgroup of patients with moderate renal impairment, −4 mg/dL in the subgroup of patients with severe renal impairment, and +44 mg/dL in the subgroup of patients with ESRD. These findings are inconclusive because the trial was not adequately powered to show efficacy within specific subgroups of renal impairment.

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Table 12: A1C at Week 12 in a Placebo-Controlled Trial of ONGLYZA in Patients with Renal Impairment*

Efficacy Parameter	ONGLYZA 2.5 mg N=85	Placebo N=85
Hemoglobin A1C (%)	**N=81**	**N=83**
Baseline (mean)	8.4	8.1
Change from baseline (adjusted mean†)	−0.9	−0.4
Difference from placebo (adjusted mean†)	−0.4‡	
95% Confidence Interval	(−0.7, −0.1)	

* Intent-to-treat population using last observation on study
† Least squares mean adjusted for baseline value
‡ p-value <0.01 compared to placebo

14.3 Cardiovascular Safety Trial

The cardiovascular risk of ONGLYZA was evaluated in SAVOR, a multicenter, multinational, randomized, double-blind study comparing ONGLYZA (N=8280) to placebo (N=8212), both administered in combination with standard of care, in adult patients with type 2 diabetes at high risk for atherosclerotic cardiovascular disease. Of the randomized study subjects, 97.5% completed the trial, and the median duration of follow-up was approximately 2 years. The trial was event-driven, and patients were followed until a sufficient number of events were accrued.

Subjects were at least 40 years of age, had A1C ≥6.5%, and multiple risk factors (21% of randomized subjects) for cardiovascular disease (age ≥55 years for men and ≥60 years for women plus at least one additional risk factor of dyslipidemia, hypertension, or current cigarette smoking) or established (79% of the randomized subjects) cardiovascular disease defined as a history of ischemic heart disease, peripheral vascular disease, or ischemic stroke.

The majority of subjects were male (67%) and Caucasian (75%) with a mean age of 65 years. Approximately 16% of the population had moderate (estimated glomerular filtration rate [eGFR] ≥30 to ≤50 mL/min) to severe (eGFR <30 mL/min) renal impairment, and 13% had a prior history of heart failure. Subjects had a median duration of type 2 diabetes mellitus of approximately 10 years, and a mean baseline A1C level of 8.0%. Approximately 5% of subjects were treated with diet and exercise only at baseline. Overall, the use of diabetes medications was balanced across treatment groups (metformin 69%, insulin 41%, sulfonylureas 40%, and TZDs 6%). The use of cardiovascular disease medications was also balanced (ACE inhibitors or ARBs 79%, statins 78%, aspirin 75%, beta-blockers 62%, and non-aspirin antiplatelet medications 24%).

The primary analysis in SAVOR was time to first occurrence of a Major Adverse Cardiac Event (MACE). A major adverse cardiac event in SAVOR was defined as a cardiovascular death or a nonfatal myocardial infarction (MI) or a nonfatal ischemic stroke. The study was designed as a non-inferiority trial with a pre-specified risk margin of 1.3 for the hazard ratio of MACE and was also powered for a superiority comparison if non-inferiority was demonstrated.

The results of SAVOR, including the contribution of each component to the primary composite endpoint, are shown in Table 13. The incidence rate of MACE was similar in both treatment arms: 3.8 MACE per 100 patient-years on placebo vs. 3.8 MACE per 100 patient-years on ONGLYZA. The estimated hazard ratio of MACE associated with ONGLYZA relative to placebo was 1.00 with a 95.1% confidence interval of (0.89, 1.12). The upper bound of this confidence interval, 1.12, excluded a risk margin larger than 1.3.

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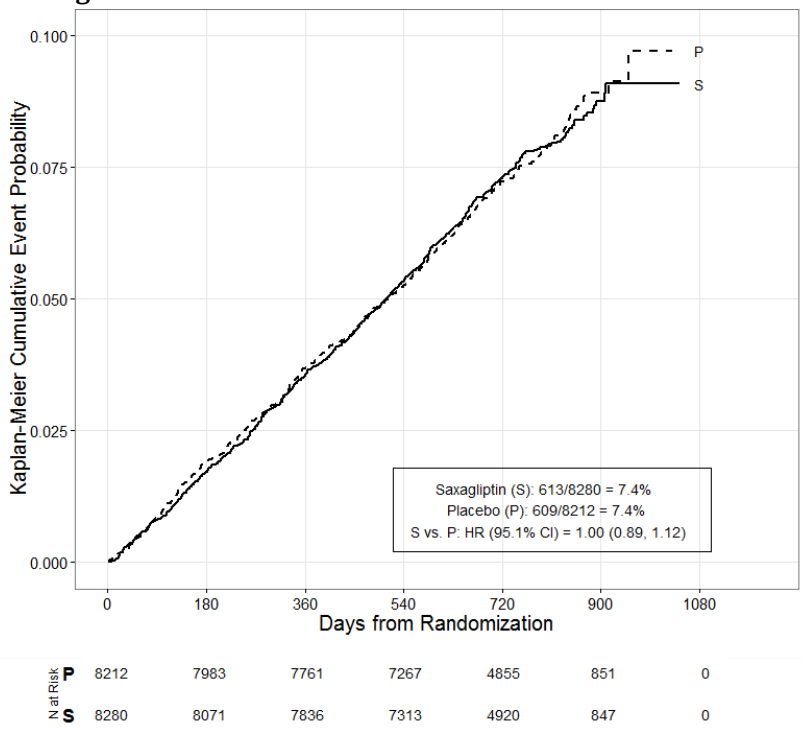
Table 13: Major Adverse Cardiovascular Events (MACE) by Treatment Group in the SAVOR Trial

	ONGLYZA		Placebo		Hazard Ratio
	Number of Subjects (%)	**Rate per 100 PY**	**Number of Subjects (%)**	**Rate per 100 PY**	**(95.1% CI)**
Composite of first event of CV death, non-fatal MI or non-fatal ischemic stroke (MACE)	**N=8280**	**Total PY = 16308.8**	**N=8212**	**Total PY = 16156.0**	
	613 (7.4)	3.8	609 (7.4)	3.8	1.00 (0.89, 1.12)
CV death	245 (3.0)	1.5	234 (2.8)	1.4	
Non-fatal MI	233 (2.8)	1.4	260 (3.2)	1.6	
Non-fatal ischemic stroke	135 (1.6)	0.8	115 (1.4)	0.7	

The Kaplan-Meier-based cumulative event probability is presented in Figure 2 for time to first occurrence of the primary MACE composite endpoint by treatment arm. The curves for both ONGLYZA and placebo arms are close together throughout the duration of the trial. The estimated cumulative event probability is approximately linear for both arms, indicating that the incidence of MACE for both arms was constant over the trial duration.

Figure 2: Cumulative Percent of Time to First MACE



Vital status was obtained for 99% of subjects in the trial. There were 798 deaths in the SAVOR trial. Numerically more patients (5.1%) died in the ONGLYZA group than in the placebo group (4.6%). The risk of deaths from all cause (Table 14) was not statistically different between the treatment groups (HR: 1.11; 95.1% CI: 0.96, 1.27).

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Table 14: All-cause mortality by Treatment Group in the SAVOR Study

	ONGLYZA		Placebo		Hazard Ratio
	Number of Subjects (%)	**Rate per 100 PY**	**Number of Subjects (%)**	**Rate per 100 PY**	**(95.1% CI)**
	N=8280	**PY=16645.3**	**N=8212**	**PY=16531.5**	
All-cause mortality	420 (5.1)	2.5	378 (4.6)	2.3	1.11 (0.96, 1.27)
CV death	269 (3.2)	1.6	260 (3.2)	1.6	
Non-CV death	151 (1.8)	0.9	118 (1.4)	0.7	

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

ONGLYZA (saxagliptin) tablets have markings on both sides and are available in the strengths and packages listed in Table 15.

Table 15: ONGLYZA Tablet Presentations

Tablet Strength	Film-Coated Tablet Color/Shape	Tablet Markings	Package Size	NDC Code
5 mg	pink biconvex, round	“5” on one side and “4215” on the reverse, in blue ink	Bottles of 30 Bottles of 90 Bottles of 500	0310-6105-30 0310-6105-90 0310-6105-50
2.5 mg	pale yellow to light yellow biconvex, round	“2.5” on one side and “4214” on the reverse, in blue ink	Bottles of 30 Bottles of 90	0310-6100-30 0310-6100-90

Storage and Handling

Store at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read FDA-approved patient labeling (Medication Guide).

Medication Guide

Healthcare providers should instruct their patients to read the Medication Guide before starting ONGLYZA therapy and to reread it each time the prescription is renewed. Patients should be instructed to inform their healthcare provider if they develop any unusual symptom or if any existing symptom persists or worsens.

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Patients should be informed of the potential risks and benefits of ONGLYZA and of alternative modes of therapy. Patients should also be informed about the importance of adherence to dietary instructions, regular physical activity, periodic blood glucose monitoring and A1C testing, recognition and management of hypoglycemia and hyperglycemia, and assessment of diabetes complications. During periods of stress such as fever, trauma, infection, or surgery, medication requirements may change and patients should be advised to seek medical advice promptly.

Pancreatitis

Patients should be informed that acute pancreatitis has been reported during postmarketing use of ONGLYZA. Before initiating ONGLYZA, patients should be questioned about other risk factors for pancreatitis, such as a history of pancreatitis, alcoholism, gallstones, or hypertriglyceridemia. Patients should also be informed that persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Patients should be instructed to promptly discontinue ONGLYZA and contact their healthcare provider if persistent severe abdominal pain occurs [*see Warnings and Precautions (5.1)*].

Heart Failure

Patients should be informed of the signs and symptoms of heart failure. Before initiating ONGLYZA, patients should be asked about a history of heart failure or other risk factors for heart failure including moderate to severe renal impairment. Patients should be instructed to contact their healthcare provider as soon as possible if they experience symptoms of heart failure, including increasing shortness of breath, rapid increase in weight or swelling of the feet [*see Warnings and Precautions (5.2)*].

Hypersensitivity Reactions

Patients should be informed that serious allergic (hypersensitivity) reactions, such as angioedema, anaphylaxis, and exfoliative skin conditions, have been reported during postmarketing use of ONGLYZA. If symptoms of these allergic reactions (such as rash, skin flaking or peeling, urticaria, swelling of the skin, or swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing) occur, patients must stop taking ONGLYZA and seek medical advice promptly.

Severe and Disabling Arthralgia

Inform patients that severe and disabling joint pain may occur with this class of drugs. The time to onset of symptoms can range from one day to years. Instruct patients to seek medical advice if severe joint pain occurs [*see Warnings and Precautions (5.5)*].

Bullous Pemphigoid

Inform patients that bullous pemphigoid may occur with this class of drugs. Instruct patients to seek medical advice if blisters or erosions occur [*see Warnings and Precautions (5.6)*].

Missed Dose

Patients should be informed that if they miss a dose of ONGLYZA they should take the next dose as prescribed, unless otherwise instructed by their healthcare provider. Patients should be instructed not to take an extra dose the next day.

Administration Instructions

Patients should be informed that ONGLYZA tablets must not be split or cut.

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Laboratory Tests

Patients should be informed that response to all diabetic therapies should be monitored by periodic measurements of blood glucose and A1C, with a goal of decreasing these levels toward the normal range. A1C is especially useful for evaluating long-term glycemic control. Patients should be informed of the potential need to adjust their dose based on changes in renal function tests over time.

ONGLYZA is a registered trademark of the AstraZeneca group of companies.

Distributed by:
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850

Product of Ireland

Reference ID: 4043030

MEDICATION GUIDE
ONGLYZA® (on-GLY-zah)
(saxagliptin)
tablets

Read this Medication Guide carefully before you start taking ONGLYZA and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or treatment. If you have any questions about ONGLYZA, ask your healthcare provider.

What is the most important information I should know about ONGLYZA?
Serious side effects can happen to people taking ONGLYZA, including:
1) Inflammation of the pancreas (pancreatitis) which may be severe and lead to death.
Certain medical problems make you more likely to get pancreatitis.
Before you start taking ONGLYZA:
Tell your healthcare provider if you have ever had

- inflammation of your pancreas (pancreatitis)
- a history of alcoholism
- stones in your gallbladder (gallstones)
- high blood triglyceride levels

It is not known if having these medical problems will make you more likely to get pancreatitis with ONGLYZA.
Stop taking ONGLYZA and contact your healthcare provider right away if you have pain in your stomach area (abdomen) that is severe and will not go away. The pain may be felt going from your abdomen through to your back. The pain may happen with or without vomiting. These may be symptoms of pancreatitis.
2) Heart failure
Before you start taking ONGLYZA:
Tell your healthcare provider if you

- have ever had heart failure or have problems with your kidneys.

Contact your healthcare provider right away if you have any of the following symptoms:

- increasing shortness of breath or trouble breathing, especially when you lie down
- swelling in the feet, ankles or legs
- an unusually fast increase in weight

These may be symptoms of heart failure.

What is ONGLYZA?

- ONGLYZA is a prescription medicine used with diet and exercise to control high blood sugar (hyperglycemia) in adults with type 2 diabetes.
- ONGLYZA lowers blood sugar by helping the body increase the level of insulin after meals.
- ONGLYZA is unlikely by itself to cause your blood sugar to be lowered to a dangerous level (hypoglycemia) because it does not work well when your blood sugar is low. However, hypoglycemia may still occur with ONGLYZA. Your risk for getting hypoglycemia is higher if you take ONGLYZA with some other diabetes medicines, such as a sulfonylurea or insulin.
- ONGLYZA is not for people with type 1 diabetes.
- ONGLYZA is not for people with diabetic ketoacidosis (increased ketones in your blood or urine).

It is not known if ONGLYZA is safe and effective in children younger than 18 years old.

Who should not take ONGLYZA?
Do not take ONGLYZA if you:

- are allergic to any ingredients in ONGLYZA. See the end of this Medication Guide for a complete list of ingredients in ONGLYZA.
  Symptoms of a serious allergic reaction to ONGLYZA may include:
  - swelling of your face, lips, throat, and other areas on your skin
  - raised, red areas on your skin (hives)
  - difficulty with swallowing or breathing
  - skin rash, itching, flaking, or peeling

If you have these symptoms, stop taking ONGLYZA and contact your healthcare provider right away.

What should I tell my healthcare provider before taking ONGLYZA?
Before you take ONGLYZA, tell your healthcare provider if you:

- have kidney problems.
- are pregnant or plan to become pregnant. It is not known if ONGLYZA will harm your unborn baby. If you are pregnant, talk with your healthcare provider about the best way to control your blood sugar while you are pregnant.
- are breast-feeding or plan to breast-feed. ONGLYZA may be passed in your milk to your baby. Talk with your healthcare provider about the best way to feed your baby while you take ONGLYZA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.
ONGLYZA may affect the way other medicines work, and other medicines may affect how ONGLYZA works. Contact your healthcare provider if you will be starting or stopping certain other types of medications, such as antibiotics, or medicines that treat fungus or HIV/AIDS, because your dose of ONGLYZA might need to be changed.

How should I take ONGLYZA?

- Take ONGLYZA by mouth one time each day exactly as directed by your healthcare provider. Do not change your dose without talking to your healthcare provider.
- ONGLYZA can be taken with or without food.
- Do not split or cut ONGLYZA tablets.
- During periods of stress on the body, such as fever, trauma, infection, or surgery.
  Contact your healthcare provider right away as your medication needs may change.
- Your healthcare provider should test your blood to measure how well your kidneys are working before and during your treatment with ONGLYZA. You may need a lower dose of ONGLYZA if your kidneys are not working well.
- Follow your healthcare provider's instructions for treating blood sugar that is too low (hypoglycemia). Talk to your healthcare provider if low blood sugar is a problem for you.
- If you miss a dose of ONGLYZA, take it as soon as you remember. If it is almost time for your next dose, skip the missed dose. Just take the next dose at your regular time. Do not take two doses at the same time unless your healthcare provider tells you to do so. Talk to your healthcare provider if you have questions about a missed dose.
- If you take too much ONGLYZA, call your healthcare provider or Poison Control Center at 1-800-222-1222, or go to the nearest hospital emergency room right away.

What are the possible side effects of ONGLYZA?
ONGLYZA can cause serious side effects, including:

- See "**What is the most important information I should know about ONGLYZA?**"
- **Allergic (hypersensitivity) reactions**, such as:
  - swelling of your face, lips, throat, and other areas on your skin
  - difficulty with swallowing or breathing
  - raised, red areas on your skin (hives)
  - skin rash, itching, flaking, or peeling

  If you have these symptoms, stop taking ONGLYZA and contact your healthcare provider right away.
- **Joint pain**. Some people who take medicines called DPP-4 inhibitors like ONGLYZA, may develop joint pain that can be severe. Call your healthcare provider if you have severe joint pain.
- **Skin reaction.** Some people who take medicines called DPP-4 inhibitors, like ONGLYZA, may develop a skin reaction called bullous pemphigoid that can require treatment in a hospital. Tell your healthcare provider right away if you develop blisters or the breakdown of the outer layer of your skin (erosion). Your healthcare provider may tell you to stop taking ONGLYZA.

Common side effects of ONGLYZA include:

- upper respiratory tract infection
- urinary tract infection
- headache

Low blood sugar (hypoglycemia) may become worse in people who also take another medication to treat diabetes, such as sulfonylureas or insulin. Tell your healthcare provider if you take other diabetes medicines. If you have symptoms of low blood sugar, you should check your blood sugar and treat if low, then call your healthcare provider. Symptoms of low blood sugar include:

- shaking
- sweating
- rapid heartbeat
- change in vision
- hunger
- headache
- change in mood

Swelling or fluid retention in your hands, feet, or ankles (peripheral edema) may become worse in people who also take a thiazolidinedione to treat diabetes. If you do not know whether you are already on this type of medication, ask your healthcare provider.

These are not all of the possible side effects of ONGLYZA. Tell your healthcare provider if you have any side effects that bother you or that do not go away. For more information, ask your healthcare provider.
Call your healthcare provider for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

How should I store ONGLYZA?

Store ONGLYZA between 68°F and 77°F (20°C and 25°C).

Keep ONGLYZA and all medicines out of the reach of children.

General information about the use of ONGLYZA

Medicines are sometimes prescribed for conditions that are not mentioned in Medication Guides. Do not use ONGLYZA for a condition for which it was not prescribed. Do not give ONGLYZA to other people, even if they have the same symptoms you have. It may harm them.
This Medication Guide summarizes the most important information about ONGLYZA. If you would like to know more information about ONGLYZA, talk with your healthcare provider. You can ask your healthcare provider for additional information about ONGLYZA that is written for healthcare professionals.

What are the ingredients of ONGLYZA?

Active ingredient: saxagliptin
Inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. In addition, the film coating contains the following inactive ingredients: polyvinyl alcohol, polyethylene glycol, titanium dioxide, talc, and iron oxides.

What is type 2 diabetes?

Type 2 diabetes is a condition in which your body does not make enough insulin, and the insulin that your body produces does not work as well as it should. Your body can also make too much sugar. When this happens, sugar (glucose) builds up in the blood. This can lead to serious medical problems.
The main goal of treating diabetes is to lower your blood sugar so that it is as close to normal as possible.
High blood sugar can be lowered by diet and exercise, and by certain medicines when necessary.

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For more information, go to www.ONGLYZA.com or call 1-800-ONGLYZA.

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